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HL

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/260,037	03/02/99	YACOBY-ZEEVI	O 910/13

HM12/0203

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EXAMINER	
HUTSON, R	
ART UNIT	**PAPER NUMBER**
1652	5

DATE MAILED: 02/03/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/260,037	Yacoby-Zeevi
Examiner	**Group Art Unit**
Richard Hutson	1652

☒ Responsive to communication(s) filed on *Nov 2, 1999*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-53* is/are pending in the applicat

Of the above, claim(s) *9-53* is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-8* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Election/Restriction

Claims 1-53 are pending.

Applicant's election without traverse of Group I, Claims 1-8 in Paper No. 4 is acknowledged.

Claims 9-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper No. 4.

Specification

The disclosure is objected to because of the following informalities: At page 30, line 5 the disclosure refers to U.S. Patent Application 09/xxx,xxx. This is improper and this number must be filled in.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Fuks et al. (US Pat No: 5,362,641).

Fuks et al. teach a substantially purified heparanase from human SK-HEP-1 cell line and a method to purify the heparanase. They teach the use of this heparanase as the basis for a pharmaceutical composition comprising the heparanase in combination with a pharmaceutically acceptible, preferrably slow releasing carrier (column 5, lines 17-30). Such a composition is useful for the treatment of wounds and enhancement of the wound-healing process. A pharmaceutically acceptible slow releasing carrier encompasses drug delivery systems such as liposomes, granules and the like as defined in the instant specification (page 30, lines 9-16).

Therefore claims 1 and 6 are anticipated by Fuks et al.

Claims 1, 2, 4 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by the Sigma Catalog (page 275, 1992).

Sigma sells and teaches the use of collagenase for the hydrolysis of native collagen in the isolation of cells from animal tissue and tissue culture. Sigma teaches the wide use of collagenase in the dissociation of tissues, specifically the release of epididymal adipocytes, hepatocytes, and pancreatic islets. Thus Sigma teaches a biological preparation comprising a biological material and the extracellular matrix degrading enzyme, collagenase, wherein the biological material is a plurality of cells or a tissue to be dissociated.

Therefore, claims 1, 2, 4 and 7 are anticipated by the Sigma Catalog.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7 and 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuks et al.and Wang et al. (J. Orthop. Res., 14 (2): 149-153 1996, abstract)

As discussed above, Fuks et al. teach a substantially purified heparanase from human SK-HEP-1 cell line and the use of this heparanase as the basis for a pharmaceutical composition useful for the treatment of wounds and enhancement of the wound-healing processes. Fuks et al. further teach that the extracellular matrix appears to be essential to the control of cell proliferation and morphogenesis and that heparan sulfate proteoglycans (HSPG), as a principal component of basement membranes plays a integral role in tissue architecture and function. A number of normal and abnormal physiological conditions and disorders are associated with the degradation of the extracellular matrix of various tissues, such as neutrophil mobilization during the inflammatory process as well as tumor cell invasion during metastasis. Thus the invading cells must be capable of producing ECM degrading enzymes in order to move through the tissue. The enzymes include in addition to heparanase, chrondroitinase, hyaluronidase and keratanase as well as other ECM degrading enzymes.

Fuks et al. teach in addition to the above function ECM degradation an additional function of heparanase is the release of growth factors from basement membranes and subendothelial ECM such as angiogenic, endothelial (ECGF) and fibroblast growth factors (FGF). FGF is essential in the proliferation of fibroblasts and virtually all other mesoderm and neuro-ectoderm-derived cells which are responsible for the production of collagen tissue. Fuks et al. teach that FGF is stored within the basement membrane and bound to heparan sulfate until an exogenous factor such as haparanase causes its release. Fuks et al. teach that heparanase may provide an effective method to mobilize and activate the ECM-bound FGF and hence promote the wound healing process as well as other pathological conditions which are likely to benefit from neovascularization promoted by FGF including cardiac, cerebral and peripheral ischaemic diseases associated with vascular damage. Other potential clinical applications for angiogenic factors taught by Fuks et al. are in processes such as ovulation, hair growth, transplantation, nerve regeneration and bone and cartilage repair.

Wang et al. teach that basic fibroblast growth factor enhances bone-graft incorporation. Specifically Wang et al. teach the implantation of bone grafts, which had been previously soaked overnight in basic fibroblast growth factor, into the proximal tibiae of recipient rats.

One of ordinary skill in the art at the time of filing would have been motivated to pretreat bone grafts prior to implantation of the grafts in recipient bone tissue with a growth factor to stimulate integration of the graft into the recipient tissue as taught by Wang et al. Based on the teaching of Fuks et al. one of ordinary skill in the art at the time of filing would have been

motivated to treat said bone grafts with heparanase as opposed to basic fibroblast growth factor in order to stimulate the release of endogenous FGF from the recipient tissue. As taught by Fuks et al., the use of heparanase to release FGF from its natural setting has the advantage of the cells responding locally to the endogenous natural growth factor and in an appropriate amount as opposed to high doses of FGF which have been shown to be toxic to various cell types including endothelial cells.

Therefore, claims 1-5, 7 and 8 are made obvious by Fuks et al and Wang et al.

Claims 3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sigma Catalog.

As discussed above, Sigma sells and teaches the wide use of collagenase for the hydrolysis of native collagen in the isolation of cells from animal tissue including epididymal adipocytes, hepatocytes and pancreatic islets. While Sigma teaches the use of collagenase specifically in the release of epididymal adipocytes, hepatocytes and pancreatic islets, its use is not limited to these cell types. Sigma teaches that their crude collagenase preparations are suitable for the isolation of cells from **many** types of animal tissues and in fact Sigma offer seven different types of collagenase preparations for this use. Thus Sigma suggests a biological preparation comprising a biological material and the extracellular matrix degrading enzyme, collagenase, wherein the biological material is a plurality of cells or a tissue to be dissociated.

One of ordinary skill in the art at the time of filing would have been motivated to use one of the Sigma crude preparations of collagenase for the release of cells including embryo, skin

flaps, bone scraps, marrow hematopoietic or stromal stem cells, keratinocytes, blastocytes, neuroblasts, astrocytes or fibroblasts or even cells which had been genetically modified based on the success of these collagenase preparations in the isolation of adipocytes, hepatocytes and pancreatic islets.

Therefore, claims 3 and 5 are made obvious by the Sigma Catalog.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Rebecca Prouty

REBECCA E. PROUTY
PRIMARY EXAMINER
GROUP 1600

Richard Hutson Ph.D.